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Review Article

UNDERSTANDING HEMODYNAMIC INCOHERENCE: MECHANISMS, PHENOTYPES, AND IMPLICATIONS FOR TREATMENT

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ABSTRACT—The reversal of microcirculation dysfunction is crucial for assessing the success of shock resuscitation and significantly influences patient prognosis. However, hemodynamic incoherence is observed when microcirculatory dysfunction persists despite the restoration of macrocirculatory function after resuscitation. Recent advancements in technology have enabled bedside assessment of microcirculation in shock patients, allowing for direct visualization of microcirculatory morphology and quantitative evaluation of its functional status. This article reviews the pathophysiological mechanisms that lead to hemodynamic incoherence. It also introduces the current understanding and classification framework for the different phenotypes of hemodynamic incoherence. Existing evidence indicates that the diverse mechanisms leading to microcirculatory disorders result in varied manifestations among patients experiencing hemodynamic incoherence, highlighting the heterogeneity of this population. Some classification frameworks have been proposed to enhance our understanding of these phenotypes. By integrating pathophysiological mechanisms, clinical symptoms, indicators of macrocirculation, microcirculation, tissue metabolism, and biomarkers, we can summarize certain clinical features of phenotypes in hemodynamic incoherence to form a conceptual framework. Additionally, strategies for creating targeted treatments based on different phenotypes require further validation.

KEYWORDS—Hemodynamic incoherence; microcirculation; macrocirculation; shock; phenotypes

INTRODUCTION

Shock, characterized by tissue hypoperfusion and impaired oxygen metabolism, can present a persistent management challenge even after systemic and regional blood flow optimization (1). The microcirculation, which includes arterioles, capillary networks, and venules with a diameter less than 100 μm, is essential for maintaining tissue perfusion. Microcirculatory dysfunction has been observed in shock patients, where despite the restoration of macrocirculatory function after resuscitation, microcirculatory impairment may persist. This phenomenon, referred to as hemodynamic incoherence, indicates a disconnect between macrocirculatory parameters—such as blood pressure and cardiac output (CO)—and microcirculation. It has been widely reported in cases of shock resulting from burns, hemorrhage, sepsis, cardiogenic issues, and other causes (2,3). Hemodynamic incoherence is believed to play a crucial role in the persistence of unresolved shock (4).

Recent advancements in techniques such as hand-held vital microscopes (HVMs) imaging have enabled the visualization of microcirculatory changes in shock patients, shedding light on the heterogeneous nature of this population with hemodynamic incoherence (5). Understanding the phenotypes of shock patients with hemodynamic incoherence is essential for appropriate management. However, there is currently no unified classification for the phenotypes of hemodynamic incoherence. In the present article, we review the pathophysiological mechanisms that lead to hemodynamic incoherence. We discuss the perspectives and evidence supporting the existence of different phenotypes in hemodynamic incoherence. We aim to summarize the clinical characteristics of various phenotypes related to hemodynamic incoherence by integrating multiple sources of information. Additionally, we provide an outlook on the potential value of targeted treatments based on the phenotype in shock patients with hemodynamic incoherence.

MECHANISMS OF HEMODYNAMIC INCOHERENCE

The blood perfusion of microcirculation is influenced by a multitude of factors, including the hemodynamics of the macrocirculation (such as CO, blood pressure), venous resistance, vascular endothelium, vasomotor response, and homeostasis of coagulation (6). In healthy conditions, these factors are finely tuned to match microcirculatory blood flow with the oxygen demands of local tissues. However, shock can disrupt this regulation through systemic and local pathways, depending on the underlying cause or disease stage, leading to microcirculation disturbance and the hemodynamic incoherence (7). The pathophysiological mechanisms leading to microcirculation disturbance under hemodynamic incoherence are described below.

Venous congestion

Blood flow through each capillary bed is regulated by the hemodynamic pressures generated between the precapillary sphincter

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and the post capillary venules. The pressure difference between the arterial and venous ends of the capillaries is typically around 15 to 30 mm Hg (8). Elevated venous pressure can result from various factors such as reduced CO, excessive fluid resuscitation, mechanical ventilation, or increased abdominal pressure. This can create back pressure that impairs blood flow from capillaries to veins, leading to microcirculatory disorders by disrupting the pressure gradient in microcirculation (6). This perspective is reinforced by the research of Vellinga *et al.*, who identified a notable correlation between elevated central venous pressure (CVP) and compromised microcirculatory blood flow (9).

Vasomotor hyperreactivity

The arterioles of microcirculation are surrounded by vascular smooth muscle and are regulated by sympathetic nerves. Excessive sympathetic activity can lead to vasoconstriction, which reduces blood flow in the microcirculation. This reduction in blood flow can negatively affect tissue perfusion and overall organ function, potentially resulting in ischemia or impaired metabolic processes (10). Shock patients may have an imbalance of sympathetic and parasympathetic nerve function at certain stages of the disease. Sympathetic nerve excitation can trigger the release of adrenaline and norepinephrine, while the inappropriate use of vasoactive drugs can further exacerbate vasoconstriction (11,12). Additionally, reduced endothelial nitric oxide synthase (eNOS) synthesis in local endothelial cells and the release of other vasoconstricting substances amplify the vasoconstrictive effects of catecholamines, leading to microcirculatory perfusion disorders despite normal systemic hemodynamics (7,13).

Vasomotor hyporeactivity

The vascular contractility in shock varies from refractoriness, to unaltered or even hyperresponsiveness, depending on the vessel and the period of disease (14). The opposite of excessive vasoconstriction in shock is vasoplegia, which is characterized by vasomotor hyporesponsiveness of blood vessels to vasoconstricting substances, severe vasodilation, and a significant decrease in systemic vascular resistance despite a normal or high cardiac index (15). The pathophysiology of vasoplegia in shock is complex, involving various mechanisms in vascular smooth muscle cells such as G protein-coupled receptor desensitization (adrenoceptors, vasopressin 1 receptors, angiotensin type 1 receptors), alteration of second messenger pathways, critical illness-related corticosteroid insufficiency, and increased production of vasodilatory mediators (nitric oxide, prostacyclin, adenosine) (16). At the microcirculatory level, vasoplegia disrupts the regulation of blood flow, leading to a redistribution of perfusion away from vital organs and tissues. High doses of vasopressors may effectively sustain systemic blood pressure; however, variations in blood vessel responses can result in inadequate blood flow to certain organs and disruptions in microcirculation (14,17).

Endothelium dysfunction

Endothelium function is influenced by endothelial cells, glycocalyx layer, and pericytes, which play a key role in microcirculatory dysfunction caused by shock (18,19). Shock-induced sympatho-adrenal activation, inflammatory cytokines, and reactive oxygen species (ROS) can lead to endothelial dysfunction and glycocalyx destruction. Nitric oxide (NO) synthesized by endothelial cells plays a crucial role in regulating blood flow of microcirculation. Decreased eNOS can result in increased sensitivity of microcirculation to vasoconstrictors, leading to decreased blood. Conversely, overexpression of inducible nitric oxide synthase (iNOS) can cause excessive vasodilation (20). In shock, the expression of nitric oxide synthase (NOS) isoforms can vary significantly across different vascular beds and even within the same organ. This heterogeneity can lead to local vasoconstriction or vasodilation abnormalities, ultimately affecting blood flow distribution in the microcirculation (20,21). This can result in tissue hypoperfusion even when systemic blood pressure is normal. Shock can also disrupt tight junctions and adherens junctions between endothelial cells, which, together with glycocalyx degradation, promote endothelial permeability (18). Pericytes, located on the outer surface of capillaries and venules, are integral to maintaining vascular stability and regulating blood flow (22). In shock states, such as septic or hemorrhagic shock, the activation of inflammatory pathways can lead to pericyte dysfunction. This dysfunction results in impaired pericyte contractility and loss of their supportive role in endothelial cell function, contributing to increased vascular permeability and capillary leakage (23). In addition, pericytes are highly responsive to inflammatory signals. When stimulated by lipopolysaccharide (LPS), interleukin-1 beta (IL-1β) or tumor necrosis factor-alpha (TNF-α), pericytes can secrete significant amounts of proinflammatory molecules and chemokines, and upregulate the expression of endothelial adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin. This enhances the interaction between inflammatory cells and the microvascular endothelium, further exacerbating the inflammatory damage to the vascular endothelial barrier (24). Increased permeability of the endothelial barrier will result in extravasation of intravascular fluids and proteins into the tissue space. Fluid resuscitation may maintain systemic blood pressure but cause tissue edema, which increases oxygen diffusion distance and affects cellular oxygen uptake (5). Furthermore, tissue edema causes an increase in tissue pressure, resulting in higher resistance in the venous outflow orifice. This, in turn, leads to a decrease in tissue perfusion pressure, ultimately resulting in microcirculatory hypoperfusion under normal macrocirculation (25,26).

Microthrombus formation

Sympatho-adrenal activation and inflammation in shock can upregulate adhesion molecules on endothelial cells, such as ICAM-1 and VCAM-1 (18). The degradation of the glycocalyx exposes these adhesion molecules, promoting the adhesion and aggregation of red blood cells, white blood cells, platelets, and endothelial cells in microvessels (19,27). This adhesion and aggregation further activate inflammation and oxidative stress, deteriorating the endothelium and glycocalyx in a vicious cycle. Activated endothelial cells with increased expression of procoagulant substances and decreased activity of anticoagulants can activate the local clotting pathway, leading to microthrombus formation in the microcirculation (28,29). Even after systemic blood pressure restoration, microcirculation may remain nonreflow due to immune microthrombus blockage, potentially resulting in refractory shock or disseminated intravascular coagulation (28,30). Given the critical role of endothelial injury in disrupting normal coagulation

processes, targeting strategies that protect the endothelium during resuscitation has emerged as a novel approach to treating coagulopathy associated with shock (19,31).

In summary, in the case of hemodynamic incoherence, venous congestion and abnormal vasomotor response can directly affect the velocity and distribution of microcirculation blood flow. Shock-induced endothelial dysfunction results in impaired vasoregulation, increased vascular permeability, activation of proinflammatory and procoagulant pathways, and microthrombus formation in the microcirculation. The variety of pathophysiological mechanisms contributing to microcirculation disorders can result in inconsistent and diverse manifestations of hemodynamic incoherence.

FRAMEWORKS FOR HEMODYNAMIC INCOHERENCE PHENOTYPES

Capillary refill time (CRT), peripheral perfusion index (PI), tissue oxygen saturation, skin mottling, transcutaneous partial pressure of oxygen, transcutaneous oxygen challenge test, and HVMs are often used to evaluate microcirculation perfusion. It is important to note that the development of HVMs technology enables us to visually observe changes in microcirculation. This advancement allows for a direct assessment of the microcirculatory state in patients experiencing shock with hemodynamic incoherence. In particularly, side stream dark field can quantitatively assess microcirculation by measuring total vessel density (TVD), proportion of perfused vessels (PPV), red blood cell velocities (RBCv), perfused vascular density (PVD), and other indicators (32). By monitoring microcirculation perfusion indicators, some researchers have proposed that shock patients with hemodynamic incoherence exhibit multiple phenotypes. They aim to identify and distinguish between these subtypes to provide tailored treatment regimens based on the specific phenotypes.

Framework 1

Professor He and his colleagues conceptually divided hemodynamic incoherence into four types based on the conditions of macrocirculation, microcirculation, and tissue oxygen metabolism (3). Type 1: After resuscitation, there is microcirculation disturbance (e.g., CRT, PI, PPV) along with significant abnormalities in tissue metabolism indicators (e.g., lactic acid). The uncoupling of macro- and microcirculation is primarily due to impaired microcirculatory functions in local blood flow, oxygen delivery (DO_2), and cellular hypoxia. Type 2: Abnormal microcirculation perfusion index is observed after resuscitation, but tissue oxygen metabolism remains normal. Type 3: In this type, cellular oxygen metabolism is dissociated from microcirculatory perfusion. Although macrocirculatory and microcirculatory perfusion are restored after resuscitation, dysfunction in cellular oxygen utilization leads to persistent metabolic abnormalities. Type 4: Both microcirculation disturbances and cellular oxygen utilization issues are present after resuscitation, resulting in abnormal microcirculation and tissue metabolism. As they noted, this theoretical classification poses challenges in clinical practice, particularly in distinguishing type 1 from type 4. This conceptual framework is significant for advancing clinical understanding of hemodynamic incoherence, highlighting that hemodynamic incoherence is a heterogeneous condition with multiple phenotypes (1).

Framework 2

Based on direct observation of the microcirculation, Ince has proposed that the loss of hemodynamic coherence including four main types of microcirculatory alterations, which cannot be detected by simply monitoring the macrocirculation (33). Type 1: Heterogeneous perfusion, mostly seen in septic patients, results from obstructed capillaries next to perfused ones, leading to uneven oxygenation of tissue cells, which is associated with the prognosis of patients (34). The heterogeneity in blood flow is believed to result from microthrombus blockages and impaired regulation of blood vessel tone due to factors such as NO and oxidative stress. This type is thought requires anti-inflammatory or vasodilators to promote blood flow. Type 2: Hemodilution, leading to a decrease in capillaries filled with red blood cells, results in inadequate oxygen delivery. Clinically, this condition has primarily been observed in patients undergoing cardiac surgery. Transfusing red blood cells to raise hemoglobin levels from 7.1 to 8.5 g/dL during these procedures has been shown to enhance the functional capillary density of the microcirculation (35). Type 3: Stasis of microcirculatory RBC flow is induced by excessive vasoconstriction or venous congestion. This condition is primarily observed in individuals receiving vasoconstrictive medications or those with elevated CVP resulting from excessive fluid resuscitation (17,36). Type 4: Microcirculatory alteration is associated with tissue edema caused by endothelium disruption. In this type of patient, fluid resuscitation based on systemic hemodynamic variables does not improve microcirculation, but rather exacerbates acidosis and tissue edema (19). Conversely, experiments demonstrate that inhibiting endothelial permeability can enhance microcirculation in a rodent model of extracorporeal resuscitation (37).

In summary, despite the variations in classification methods, an increasing number of researchers acknowledge that hemodynamic incoherence is a heterogeneous disease. Visualization technologies utilizing HVMs to differentiate the phenotypes of hemodynamic incoherence based on the diverse manifestations of microcirculation demonstrate significant application potential.

CLINICAL IDENTIFICATION OF PHENOTYPES

In clinical practice, the primary observation window for HVMs is sublingual microcirculation, but it has limitations. It mainly reflects local blood flow and may not accurately indicate systemic microcirculation. Motion artifacts, image quality, and operator variability can also affect the accuracy, making it challenging to identify phenotypes of hemodynamic incoherence using this method alone (38,39). Therefore, a reasonable approach is to integrate pathophysiology, clinical symptoms, hemodynamic parameters of macrocirculation, tissue metabolic indicators, biological markers and microcirculation monitoring results to provide more information for clinical identification of phenotypes of hemodynamic incoherence, thereby improving clinical operability. Based on the five pathophysiological mechanisms leading to hemodynamic incoherence described earlier in this article, we can review existing research evidence from the perspective of multimodal monitoring (Fig. 1) and summarize the clinical characteristics of different phenotypes associated with hemodynamic incoherence.

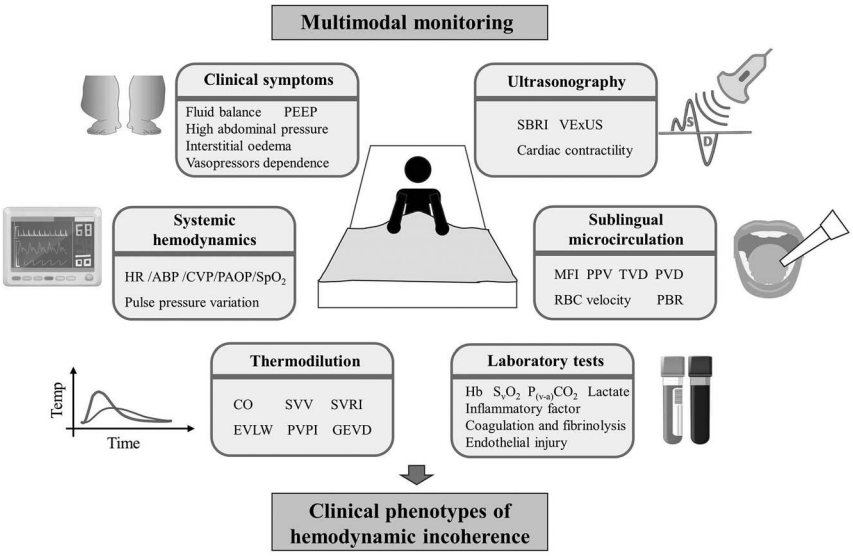

FIG. 1. **Multimodal monitoring to identify the specific phenotype of microcirculatory disorders in shock patients with hemodynamic incoherence.** Patients' clinical features, systemic hemodynamic parameters, ultrasonography, biochemical markers, and microcirculation need to be integrated into a comprehensive judgment. ABP, arterial blood pressure; CO, cardiac output; CVP, central venous pressure; EVLW, extravascular lung water; GEVD, global end-diastolic volume; Hb, hemoglobin; HR, heart rate; MFI, microcirculatory flow index; PAOP, pulmonary artery obstruction pressure; PBR, perfused boundary region; PEEP, positive end-expiratory pressure; PPV, proportion of perfused vessels; PVD, perfused vessel density; PVPI, pulmonary vascular permeability index; RBC, red blood cell; SBRI, snuffbox resistive index; SVRI, systemic vascular resistance index; SVV, stroke volume variation; TVD, total vessel density; VexUS, venous excess ultrasound.

Clinical phenotype 1

The mechanism for this phenotype is venous congestion. This type is commonly seen in patients with right ventricular dysfunction, fluid overload, high abdominal pressure, or mechanical ventilation with high positive end expiratory pressure (36,40). Patients with this phenotype may exhibit an elevated CVP or ultrasound findings suggestive of venous congestion (41). Sublingual microcirculatory imaging reveals severe deterioration of microcirculation with decreased microcirculatory flow index, severe stasis of red blood cells, and severe congestion and distention of the venules (Video S1, http://links.lww.com/SHK/C193) (36,42). This change in sublingual microcirculation represents a Type 3 condition in Professor Ince's classification framework, specifically microcirculation dysfunction due to increased venous pressure (33). Previous study has found that CVPs exceeding 12 mm Hg may reduce microcirculation perfusion by inducing increasing postcapillary pressure (9). Therefore, patients of this type can be effectively treated by reducing volume load, improving cardiac function, downregulating PEPP, lowering intra-abdominal pressure, or other means to eliminate venous congestion.

Clinical phenotype 2

This phenotype is characterized by increased vascular permeability resulting from endothelial dysfunction, which leads to intravascular fluid extravasation and tissue edema. It is commonly observed in patients with severe burns and septic shock (43,44). Patients typically present with capillary leakage syndrome, including intravascular fluid loss, hypoproteinemia, anasarca, pulmonary edema, intestinal edema, and other related symptoms (45). These patients often require a continuous positive fluid balance to maintain hemodynamics, as achieving conventional resuscitation goals may be challenging for CVP. The pulmonary vascular permeability index, measured through transpulmonary thermodilution (TPTD), can aid in assessing local pulmonary vascular permeability. A pulmonary vascular permeability index exceeding 3 indicates an increase in pulmonary vascular permeability. Elevated levels of serologic markers such as angiopoietin-2, syndecan-1, and heparan sulfate suggest endothelial injury. Furthermore, an increased vascular leakage index is positively correlated with the risk of mortality (45). Using stream dark field imaging, a decrease in TVD was observed along with an increase in the perfused boundary region, indicating a reduction in the thickness of the glycocalyx (Video S2, http://links.lww.com/SHK/C194) (46,47). The microcirculation changes observed in these patients align with the Type 4 alteration proposed by Ince (33). Patients with this phenotype may benefit from restricted fluid resuscitation, as well as albumin infusion, phosphodiesterase-4 inhibitors, vitamin C, and other treatments that protect the endothelium (45,48). Additionally, plasma exchange and fresh frozen plasma have been shown to reduce glycocalyx and endothelial damage, as well as endothelial permeability in patients experiencing shock (19,49,50). Therefore, these treatment options may hold significant potential for patients with this clinical phenotype.

Clinical phenotype 3

The pathophysiological mechanism underlying this phenotype is vasomotor hyperreactivity and excessive vasoconstriction, which can be induced by heightened sympathetic activity and inappropriate use of vasoactive drugs (11,51). Despite the presence of normal blood pressure or hypertension, the patient also displays signs of shock, including tissue hypoperfusion and acidosis (52). The snuffbox resistive index measured by ultrasonic Doppler or the systemic vascular resistance measured by TPTD can indicate elevated peripheral vascular resistance (52,53). Microcirculation was characterized by a decrease in functional and structural capillary density (Video

S3, http://links.lww.com/SHK/C195) (51,54,55). This change in microcirculation corresponds to another type 3 alteration identified by Ince, specifically, microcirculatory disturbance caused by increased arterial vascular resistance. It has been reported that pressor drugs may worsen microcirculation in some patients (56). Animal experiments have shown that dexmedetomidine, a sedative with antisympathetic activity, can improve microcirculatory blood flow in septic shock (57). Therefore, these patients may require treatment with carefully optimized vasoconstrictors or a combination of antisympathetic and vasodilator therapy (51,58).

Clinical phenotype 4

The mechanism of the fourth clinical phenotype involves the conversion of endothelial cells to a procoagulant/proinflammatory state, along with the breakdown of the glycocalyx, ultimately resulting in microthrombus formation in the microcirculation that block blood flow (31). The patients can display signs of inflammatory activation, including elevated levels of C-reactive protein, procalcitonin, and interleukin-6 in some cases. There may be also a significant increase in leukocyte count and a drop in platelets in the blood samples (59). Plasma biomarkers such as thrombomodulin, hyaluronan, and syndecan-1 were elevated, suggesting endothelial activation and glycocalyx damage (60). Fibrin/fibrinogen degradation products, D-dimer, thrombin-antithrombin complex, and other biomarkers, along with thromboelastography, may indicate an imbalance in coagulation and fibrinolysis (29,61). Microcirculation assessments reveal disrupted blood flow and heterogeneous manifestations resembling Ince's type 1 alteration (62). There is a significant rise in microcirculatory leukocytes within capillary-postcapillary venule units, indicated by filling defects. Furthermore, the presence of an RBC microaggregate suggests the occurrence of RBC clumping within the capillary vessel (Video S4, http://links.lww.com/SHK/C196) (59,63). Patients exhibiting this phenotype may benefit from anticoagulation therapies such as heparin, protein C, and thrombomodulin, as well as antiplatelet therapy. Additionally, treatment with glucocorticoids, anti-IL-6 receptor antibodies, and hemoperfusion can help reduce the inflammatory response. Administration of albumin infusion and vitamin C to protect the vascular endothelium and glycocalyx may also have a beneficial impact (64).

Clinical phenotype 5

The fifth phenotype in shock patients is primarily attributed to vasomotor hyporeactivity and vasoplegia, which can manifest in various advanced shock states, such as septic, cardiogenic, hemorrhagic, and anaphylactic shock (65). If vasoconstrictor therapy was not administered, the snuffbox resistive index or TPTD monitoring results will show a notable decrease in peripheral vascular resistance in the patient (15). Following optimization of systemic hemodynamics, patients typically present with a cardiac index exceeding 2.3 L/min/m^2 or central venous oxygen saturation above 70%, in conjunction with CVP exceeding 8 mm Hg and a mean arterial pressure ranging from 55 to 70 mm Hg. Patients require high doses of vasopressors, often exceeding 0.2 μg/kg/min norepinephrine or an equivalent dose of another vasopressor (66). In severe cases, patients may become unresponsive to vasoconstricting agents and ultimately succumb to refractory hypotension. In cases of vasodilation, microcirculation in these patients typically shows normal TVD and normal or increased blood flow velocity under high doses of vasoconstrictors (Video S5, http://links.lww.com/SHK/C197) (51,67). Treatment may involve the use of various vasopressors, such as angiotensin II and vasopressin, to maintain microcirculation perfusion. Additionally, drugs like methylene blue and hydroxocobalamin, which restore blood vessel sensitivity to vasopressors, may be beneficial for these patients (65,68).

In summary, with the promotion of HMVs application, more evidence supports the classification framework proposed by Ince. On this basis, if the characteristics of microcirculation are combined with other clinical indicators for multimodal monitoring, it will be helpful to further refine the identification of patients with hemodynamic incoherence in clinical practice. Therefore, based on the above evidence, we believe that there are at least five significant clinical phenotypes for hemodynamic incoherence. To facilitate memory and understanding, we have named these five clinical phenotypes based on their pathophysiological mechanisms: stasis (S), leakage (L), occlusion (O), obstruction (O), and paralysis (P). Collectively, they are referred to as the conceptual framework of the SLOOP phenotypes (Table 1). However, the second type proposed by Ince, which involves microcirculatory disturbance caused by hemodilution, has also been formally observed clinically (35). This alteration is attributed to anemia and can be easily identified through routine blood tests. It is often corrected by blood transfusion during the resuscitation of macrocirculation. Therefore, we have not included it in our framework. It should be emphasized that this classification framework is only a summary of the existing evidence, and as clinicians' understanding deepens, new clinical phenotypes may be proposed to improve our framework in the future.

Connections between clinical phenotypes

Hemodynamic incoherence can be observed in shock with different causes. The pathophysiological mechanisms of shock with hemodynamic incoherence caused by various etiologies or at different stages are not the same, so the five clinical phenotypes mentioned above can occur in different types of shock or at different stages of shock. These five phenotypes are interconnected and not isolated from each other. Sympathetic excitation is an initial compensatory response in the early stages of shock, which may lead to occlusion phenotypes in tissues like the skin and intestine (16,69). If shock is not corrected, sympathetic excitation can promote endothelial damage, and tissue microcirculation may evolve from the occlusion phenotype to leakage or paralysis phenotype (70). In the treatment of hemodynamic incoherence, inappropriate treatment such as excessive fluid resuscitation may cause stasis phenotype (9). If leakage and other phenotypes are not effectively or appropriately treated, they can exacerbate microcirculatory endothelial injury, ultimately leading to blood flow stagnation and microthrombosis in the microcirculation (29). This progression can result in the development of obstruction phenotype in the microcirculation. Therefore, timely recognition and swift correction of shock, along with protecting microcirculatory endothelial function, are crucial in preventing the occurrence and progression of hemodynamic incoherence (19,29).

TREATMENT STRATEGIES AND OUTLOOK

Currently, there is a broad consensus on resuscitation strategies for systemic hemodynamics in shock patients (71). But the

Table 1. **Characteristics of the SLOOP phenotypes under hemodynamic incoherence**

Phenotype	Clinical symptoms	Systemic hemodynamics	Laboratory tests	Ultrasonography	Sublingual microcirculation
Stasis (Clinical phenotype 1)	Right ventricular dysfunction Ventilation with PEEP Excessive fluid resuscitation Abdominal pressure ↑	CVP ↑	None	VExUS score ↑ Pulmonary artery hypertension Tricuspid regurgitation Right ventricular dilation	MFI ↓ Stasis of red blood cells Congestion and distention of the venules
Leakage (Clinical phenotype 2)	Interstitial edema Liquid dependence	EVLW ↑ PVPI ↑ Target CVP (challenging to maintain)	Hypoproteinemia Inflammatory factors (e.g., WBC, CRP, IL-6) ↑ Endothelial biomarkers (e.g., angiopoietin-2, syndecan-1, thrombomodulin) ↑ Vascular leakage index ↑	Tissue edema (e.g., intestines and lungs)	TVD↓ PVD↓ PBR ↑
Occlusion (Clinical phenotype 3)	Vasopressors use Sympathetic activity ↑	ABP (normal or hypertension) SVRI↑	Acidosis	SBRI ↑	TVD↓ PVD↓ Stand-still of flow
Obstruction (Clinical phenotype 4)	Abnormal TEG Thrombocytopenia DIC	None	Inflammatory factors (e.g., WBC, CRP, IL-6) ↑ Endothelial biomarkers (e.g., angiopoietin-2, syndecan-1, thrombomodulin) ↑ Coagulation biomarkers (e.g., D-dimer, thrombin-antithrombin complex) ↑	None	Heterogeneous perfusion Filling defects RBC microaggregate PBR ↑
Paralysis (Clinical phenotype 5)	Vasopressors dependence	SVRI↓(without treatment)	None	SBRI ↓ (without treatment)	Normal TVD or PVD Blood flow velocity (normal or increased)

ABP, arterial blood pressure; CRP, C-reactive protein; CVP, central venous pressure; DIC, disseminated intravascular coagulation; EVLW, extravascular lung water; MFI, microcirculatory flow index; PBR, perfused boundary region; PEEP, positive end-expiratory pressure; PVD, perfused vessel density; PVPI, pulmonary vascular permeability index; RBC, red blood cell; SBRI, snuffbox resistive index; SVRI, systemic vascular resistance index; TVD, total vessel density; TEG, thromboelastography; VexUS, venous excess ultrasound; WBC, white blood cell.

real challenge lies in those patients who do not recover from shock after optimizing the macrocirculation. In the future, the treatment of shock will involve macrocirculation, microcirculation, and cellular metabolism, which will include the whole process of oxygen delivery and utilization (Fig. 2). We can first optimize the macrocirculation according to mixed venous oxygen saturation (S_VO_2), the arteriovenous carbon dioxide gradient ($P_{(v-a)}CO_2$), CO, and other indicators. If the patient's shock cannot be improved, it indicates that the patient is experiencing hemodynamic incoherence. At this time, the clinical phenotype of the patient's hemodynamic incoherence should be identified by combining various indicators. Our SLOOP conceptual framework can provide a reference for clinicians in the identification of hemodynamic incoherence. Based on the pathophysiological mechanisms underlying each clinical phenotype, precise treatment should be administered. It is important to note that mitochondrial dysfunction is considered a universal feature of shock in subcellular structures (72). Following resuscitation, while oxygen supply to the tissue may be ensured by macrocirculation and microcirculation, mitochondrial distress could impair tissue oxygen utilization, posing challenges in reversing shock (1). Therefore, the treatment of mitochondrial dysfunction will also increasingly be integrated into the overall management of shock resuscitation as technology advances, as discussed in detail in other review (73).

Recent findings from the Direct Assessment of Microcirculation in Shock trial have shown that microcirculation-oriented resuscitation does not improve outcomes in shock patients (74). One possible reason is that the study population included patients with hemodynamic incoherence that affected the treatment response. At present, there is a lack of research evidence to evaluate the effectiveness of treatment options based on clinical phenotypes. However, as we mentioned earlier, many treatments show potential applications depending on the different pathophysiological mechanisms that cause hemodynamic incoherence. In the future, further evaluation of these treatment options is needed for shock patients with a specific phenotype of hemodynamic incoherence.

The Swan-Ganz catheter has been used since the 1970s to optimize the resuscitation of macrocirculation. Our understanding of shock now has shifted toward the microcirculation, akin to a sloop navigating into new oceans. The visual information provided by HVMs supports phenotypic identification of hemodynamic incoherence. But quantitative measures of microcirculation, such as PVD and PPV, still lack generally accepted clinical reference (5). While some previously published data may provide some clues, appropriate reference values for each phenotype remain to be determined. Therefore, the SLOOP framework is only a qualitative description of the different clinical phenotypes of hemodynamic incoherence. Sublingual microcirculation, while a valuable window for monitoring, may not fully represent the microcirculation of other tissues. Future monitoring utilizing multiple windows may provide a more comprehensive view of tissue-specific microcirculation phenotypes.

CONCLUSIONS

Hemodynamic incoherence in shock patients involves diverse pathophysiological mechanisms, leading to a variety of phenotypes. Some classification frameworks have been proposed to

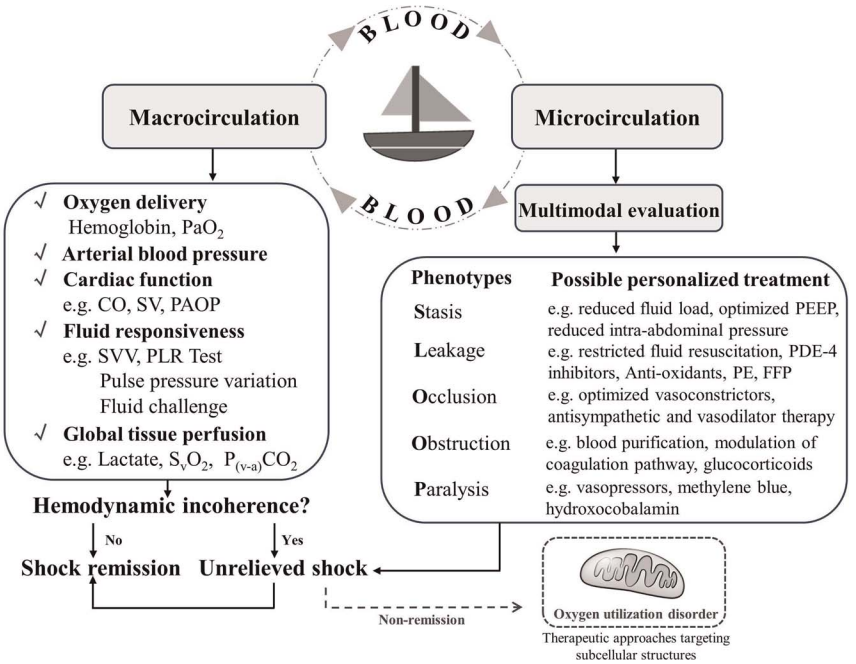

FIG. 2. **Proposal for an algorithm for the treatment of shock patients.** First, according to the monitoring parameters of the macrocirculation, the systemic hemodynamics were optimized to ensure that the patients had sufficient cardiac output and blood volume. Attention is needed to correct anemia and hypoxemia so that the macrocirculation provides adequate blood flow and oxygen to the microcirculation. If the patient's shock does not improve, there is hemodynamic incoherence. At this time, the phenotype of hemodynamic incoherence can be determined by multimodal monitoring, and then personalized treatment means can be adopted to restore the coherence of macrocirculation and microcirculation. With the advancement of technology, monitoring and treatment methods for oxygen utilization impairment induced by subcellular structural injury may be popularized in the future. CO, cardiac output; FFP, fresh frozen plasma; PAOP, pulmonary artery obstruction pressure; PDE-4, phosphodiesterase-4; PE, plasma exchange; PEEP, positive end-expiratory pressure; PLR, passive leg raising; SV, stroke volume; SVV, stroke volume variation.

enhance our understanding of these phenotypes. Current evidence supports the existence of multiple clinical phenotypes associated with hemodynamic incoherence. By integrating pathophysiological mechanisms with multimodal monitoring techniques, we can summarize and categorize these phenotypic clinical features into a new framework called SLOOP. Future research should focus on tailoring treatments based on the distinct phenotypes of hemodynamic incoherence.

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